Amendments to the Specification:

Please replace paragraph [0074] with the following amended paragraph:

[0074] Other carriers include T-cell epitopes that bind to multiple MHC alleles, *e.g.*, at least 75% of all human MHC alleles. Such carriers are sometimes known in the art as "universal T-cell epitopes." Exemplary carriers with universal T-cell epitopes include:

Influenza Hemagglutinin: $HA_{307-319}$	PKYVKQNTLKLAT (SEQ. ID NO. 11)
PAN-DR Peptide (PADRE peptide)	AKXVAAWTLKAAA (SEQ. ID NO. 12)
Malaria CS: T3 epitope	EKKIAKMEKASSVFNV (SEQ. ID NO. 13)
Hepatitis B surface antigen: HB_sAg_{19-28}	FELLTRILTI (SEQ. ID NO. 14)
Heat Shock Protein 65: $hsp65_{153-171}$	**D**QSIGDLIAEAMDKVGNEG (SEQ. ID NO. 15)
Bacillus Calmette-Guerin (BCG)	QVHFQPLPPAVVKL (SEQ. ID NO. 16)
Tetanus toxoid: $TT_{830-844}$	QYIKANSKFIGITEL (SEQ. ID NO. 17)
Tetanus toxoid: $TT_{947-967}$	**F**NNFTVSFWLRVPKVSASHLE (SEQ. ID NO. 18)
HIV gp120 T1:	KQIINMWQEVGKAMY (SEQ. ID NO. 19)
CRM_{197}	*See* the Brief Description of the Sequences (SEQ ID NO.:40)
Albumin fragment	ISQAVHAAHAEINEAGR (SEQ ID NO: 41)

Please replace paragraph [0086] with the following amended paragraph:

[0086] Aβ has several natural occurring forms. The human forms of Aβ are referred to as Aβ39, Aβ40, Aβ41, Aβ42 and Aβ43. The sequences of these peptides and their relationship to the APP precursor are illustrated by Figure 1 of Hardy et al., TINS 20, 155-158 (1997). For example, Aβ42 has the sequence:

H_2N-Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-
His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-
Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-I[[I]]**I**e-Ala-OH
(SEQ ID NO. 21).

Aβ41, Aβ40 and Aβ39 differ from Aβ42 by the omission of Ala, Ala-Ile, and Ala-Ile-Val respectively from the C-terminal end. Aβ43 differs from Aβ42 by the presence of a threonine residue at the C-terminus.

Please replace paragraph [0105] with the following amended paragraph:

[0105] Examples of such immunogenic heterologous peptides include:

Aβ 1-7/Tetanus toxoid 830-844 in a MAP4 configuration:

DAEFRHD-QYIKANSKFIGITEL (SEQ ID NO.:22)

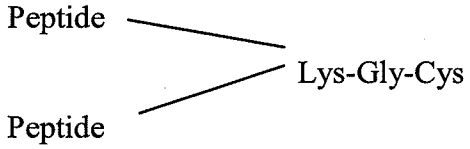
Aβ 1-7/Tetanus toxoid 947-967 in a MAP4 configuration:

DAEFRHD-FNNFTVSFWLRVPKVSASHLE (SEQ ID NO.:23)

Aβ 3-9/Tetanus toxoid 830-844 in a MAP4 configuration:

EFRHDSG-QYIKANSKFIGITEL (SEQ ID NO.:25)

DAEFRHD-QYIKANSKFIGITEL **(SEQ ID NO:22)** on a 2 branched resin



Please replace paragraph [0157] with the following amended paragraph:

[0157] Prior to conjugation, the peptides were reacted with 5,5'-dithio-bis(2-nitrobenzoic acid) [Ellman's reagent] to verify the content of free-SH groups (between 62-88% reduced). For the first four Aβ peptides (amino acids 1-7 without linker, amino acids 1-12 with GAGAC linker **(SEQ ID NO:55)**, amino acids 1-9 with GAGAC linker **(SEQ ID NO:55)**, and amino acids 1-7 with GAGAC linker **(SEQ ID NO:55)**), approximately 8.0 – 10.0 mg of peptide was dissolved in sterile distilled water to an approximate concentration of 20 mg/ml. The peptide was slowly added to cold activated CRM_{197} in a 1:1 ratio (w/w) and the pH was adjusted to approximately 7.0-7.2 with the addition of 20-36 µl of 1 N NaOH. The resulting material was gently mixed overnight at 4°C in the dark followed by dialysis in the dark against two 1L changes of PBS, pH 7.2. For the next four Aβ peptides (amino acids 1-5 without linker, amino acids 1-9 without linker, amino acids 1-12 without linker, and amino acids 1-5 with linker), reaction with Ellman's reagent was used to verify the free -SH groups. CRM_{197} was bromoacetylated, purified, and reacted with TNBSA as previously described. The pH of each peptide was adjusted to 7.0 with the addition of 0.1 M $NaPO_4$ (pH 8.5) at 2.2x the volume of the dissolved peptide. The peptide was slowly added to cold activated CRM_{197} in a 1:1 ratio and allowed to react overnight at 4°C in the dark. The resulting material was dialyzed. A final control peptide (1-12mer in reverse orientation) was conjugated to CRM_{197} as described above with the following modification. Rather than adjusting the pH of the peptide to 7.0, the pH of the activated CRM_{197} was adjusted to approximately 7.5 with the addition of 20% (v/v) 0.5 M $NaPO_4$ (pH 8.0). Each conjugate, after dialysis, was transferred into a sterile 15mL polypropylene tube, wrapped in aluminum foil, and stored at 4°C. Activation of the reactive amino residues on the carrier was then subsequently verified using mass spectrometry.

Conjugate	**Immunogenic Peptide**
Aβ1-5-C-CRM_{197}	DAEFR-C (SEQ. ID. NO.:1)
Aβ1-7-C-CRM_{197}	DAEFRHD-C (SEQ. ID NO.:2)
Aβ1-9-C-CRM_{197}	DAEFRHDSG-C (SEQ ID NO:3)
Aβ1-12-C-CRM_{197}	DAEFRHDSGYEV-C (SEQ ID NO:4)
Aβ1-5-L-C-CRM_{197}	DAEFR-GAGA-C (SEQ ID NO.:5)

Aβ 1-7-L-C-CRM_{197}	DAEFRHD-GAGA-C (SEQ ID NO.:6)
Aβ1-9-L-C-CRM_{197}	DAEFRHDSG-GAGA-C (SEQ ID NO.:7)
Aβ1-12-L-C-CRM_{197}	DAEFRHDSGYEV-GAGA-C (SEQ ID NO.:8)
Aβ12-1-C-CRM_{197} (-VE CONTROL)	VEYGSDHRFEAD-C (SEQ ID NO.: 9)

L= linker (GAGA) (SEQ ID NO.:10)

EXAMPLE 2

Preparation of Aβ Peptide-CRM_{197} Conjugate and Purification By Ultrafiltration

Bromoacetylation of CRM_{197}

Please replace paragraph [0177] with the following amended paragraph:

[0177] Peptides spanning N-terminal residues 1-5, 1-7, 1-9, and 1-12 of Aβ (with and without the linker sequence GAGAC **(SEQ ID NO:55)**) and a peptide corresponding to the N-terminus of Aβ in reverse sequence from amino acid twelve to amino acid one (1-12mer in reverse sequence), each conjugated to CRM_{197}, were used to immunize mice along with an unconjugated Aβ 1-12 mer peptide in a formulation with STIMULON™ QS-21. Each group of mice was immunized subcutaneously with a dose of either 30 μg or 5 μg of one of the samples formulated with 20 μg of the adjuvant STIMULON™ QS-21, at the beginning of the study (week 0) and subsequently at weeks 3 and 6. The study protocol is illustrated in Table 3.

Please replace paragraph [0178] with the following amended paragraph:

[0178] As shown in Table 3, peptides spanning N-terminal residues 1-5, 1-7, 1-9, and 1-12 of Aβ (with and without the linker sequence GAGAC **(SEQ ID NO:55)**) and a peptide corresponding to the N-terminus of Aβ in reverse sequence from amino acid twelve to amino acid one (1-12mer in reverse) conjugated to CRM_{197} were used to immunize mice along with unconjugated Aβ 1-12 mer peptide in a formulation with QS-21. Each group of mice was vaccinated subcutaneously with a dose of either 30 μg or 5 μg of one of the samples formulated with 20 μg of the adjuvant QS-21, at the beginning of the study (week 0) and subsequently at

weeks 3 and 6. Swiss Webster mice were used for the entire study with 5 mice in each group. Injection volume = 100 µl; B = Bleed; V = vaccinate; E = exsanguinate.

Please replace paragraph [0181] with the following amended paragraph:

[0181] Tables 4-6 illustrate end point ELISA titers against Aβ. Following primary immunization, all eight conjugates (excluding the negative control) induced measurable anti-Aβ IgG immune responses. However, the 30µg dose, but not the 5µg dose, of Aβ gave a positive response at week 3 following primary immunization. Among all the conjugates, it appears that Aβ 1-7 peptide conjugated without linker elicited as good as or better response than other conjugates studied. At 5µg dose, Aβ 1-5C did better at weeks 8-16. Aβ 1-7C was best at 30µg dose. Analysis of antibody titers after second and third immunization with either 5 or 30µg dose indicate that the maximal immune response to Aβ for most of the conjugates was seen after the second immunization. At least in mice, the third immunization did not appear to enhance the immune response. Aβ peptide however, needed three immunizations with the 30µg dose to reach maximal immune response against the peptide (Table 5). In terms of antibody decay over an extended period of time, the antibody level from the groups immunized with conjugates was reduced by 2 to 3 fold as compared to the highest level within that group. Individual samples from weeks 6 and 8 were analyzed to calculate GMTs against Aβ for each of the group (Table 6) to see if any conjugate group was substantially better than the others. Statistical analysis of week 6 titers from Aβ1-5C, Aβ 1-7C and Aβ 1-9C conjugates indicated that the Aβ 1-7 conjugate induced a significantly higher titer. It is also evident from this experiment that the linker sequence GAGAC **(SEQ ID NO:55)** did not contribute to enhancing the immune response to the peptide.

Table 4

Group	*Week 0*	**Week 3**	**Week 6**	**Week 8**	**Week 13**	**Week 16**
1-5C	<100	14,960	687,691	882,012	625,208	771,828
1-7C	<100	51,253	1,280,181	860,463	520,060	571,043
1-9C	<100	18,615	1,008,872	622,325	348,967	380,755
1-12C	<100	615	132,009	390,624	166,162	184,170
1-5LC	<100	4,999	458,075	454,631	237,573	220,091
1-7LC	<100	17,693	849,170	842,402	446,089	400,536
1-9LC	<100	18,544	1,465,115	1,180,347	571,127	579,477
1-12LC	<100	12,664	908,360	598,867	368,101	316,075
CRM_{197}	<100	<100	<100	<100	<100	<100
1-42	<100	<100	<100	<100	<100	<100
1-12	<100	<100	<100	<100	<100	<100
12-1C	<100	<100	<100	<100	<100	<100

Table 4. Weeks 0, 3, 6, 8, 13, and 16 ELISA endpoint titers against Aβ using antiserum from 5 μg dose of peptide conjugates spanning varying lengths of the N-terminus of Amyloid Aβ peptide. Ref: Elan hyperimmune polyclonal #592 = 3,073,307. Endpoint at O.D. 0.1 AU. Swiss Webster mice were immunized SC-N with 5 μg of above antigens formulated with 20 μg STIMULON™ QS-21 at weeks 0, 3, and 6.

Table 5

Group	Week 0	Week 3	Week 6	Week 8	Week 13	Week 16
1-5C	<100	18,150	590,355	332,832	204,645	176,159
1-7C	<100	100,672	1,840,741	647,470	592,638	779,072
1-9C	<100	18,520	1,184,696	713,494	363,459	327,065
1-12C	<100	7,837	1,325,725	1,126,389	681,268	577,604
1-5LC	<100	16,347	469,191	184,077	177,358	164,680
1-7LC	<100	47,866	971,229	462,200	463,466	529,726
1-9LC	<100	59,002	921,544	787,273	405,023	500,468
1-12LC	<100	27,348	697,150	483,320	284,800	397,816
CRM_{197}	<100	<100	<100	<100	<100	<100
1-42	<100	160	3,327	109,718	48,646	27,901
1-12	<100	<100	<100	<100	<100	<100
12-1C	<100	<100	<100	<100	<100	<100

Table 5. Weeks 0, 3, 6, 8, 13, and 16 ELISA endpoint titers against Aβ using antiserum from 30 μg dose of peptide conjugates spanning varying lengths of the N-terminus of Amyloid Aβ peptide. Ref: Elan hyperimmune polyclonal #592 = 3,073,307. Endpoint at O.D. 0.1 AU. Swiss Webster mice were immunized SC-N with 30 μg of above antigens formulated with 20 μg STIMULON™ QS-21 at weeks 0, 3, and 6.

Table 6

Group	Week 6	Week 8
1-5C	237,668 [a]	161,671 [b]
1-7C	1,866,702 [a]	881,146 [b]
1-9C	963,323 [a]	595,414 [b]
1-12C	940,260	955,470
1-5LC	395,553	141,084
1-7LC	516,921	394,521
1-9LC	826,773	562,458
1-12LC	544,768	376,952
1-42	365	4,565

Table 6. Weeks 6 and 8 ELISA endpoint GMTs against Aβ using antisera from 30 μg dose of peptide conjugates spanning varying lengths of the N-terminus of Amyloid-Aβ. Ref: Elan Hyperimmune Polyclonal #592 = 3,073,307. Endpoint at O.D. 0.1 AU. Swiss Webster mice were immunized SC-N with 30 μg of above antigens formulated with 20 μg STIMULON™ QS-21 at weeks 0, 3, and 6

a. Statistical analysis of week 6 titers from 1-5C, 1-7C, and 1-9C using Tukey-Kramer show a statistical difference between 1-5C vs 1-7C only, whereas, analysis using Student's T-test shows a statistical difference between 1-5C vs 1-7C and 1-5C vs 1-9C.

b. Statistical analysis of week 8 titers from 1-5C, 1-7C, and 1-9C does not show a statistical difference among the three groups. However, there appears to be a trend that may indicate a difference between 1-5C vs 1-7C.

PDAPP Mouse Brain Tissue Staining

Please replace paragraph [0182] with the following amended paragraph:

[0182] The PDAPP brain tissue staining assay provides an indication of the functionality of the Aβ peptide conjugates and/or Aβ 1-42 antiserum. Serum samples from individual mouse groups were separately analyzed for their ability to recognize PDAPP mouse brain tissue plaques containing amyloid peptide. The results are shown in Table 7A and 7B. With the exception of the Aβ 5mer conjugate antisera, there was a dose-related response in recognizing the plaques. Independent of the linker, 30μg conjugate-induced antisera had better reactivity patterns as compared to that of 5μg conjugate antisera. However, with the Aβ 5mer conjugate antisera, there seems be similar or better reactivity for the 5μg group. Comparing all these results, it is concluded that conjugates made from Aβ 1-5 mer through Aβ 1-9 mer are sufficient in eliciting plaques recognizing immune response in mice and the presence of linker is not essential. The following conclusions can be drawn from this study: (a) All of the peptide conjugates induced high titered antiserum against the carrier protein CRM_{197} to equal or slightly higher levels as compared to the unconjugated CRM_{197} control (not shown). (b) The conjugates with the GAGAC linker **(SEQ ID NO:55)** did not enhance immunogenicity or functionality compared to conjugates without the linker. (c) The immunogenicity data and PDAPP brain tissue staining (an initial indication of functional antibody) show that the Aβ 1-5mer and Aβ 1-7mer conjugates appeared to be the preferred immunogens for further development.

Table 7A. PDAPP mouse brain tissue staining.

5 µg Dose					
Without Linker			**With Linker**		
Vaccine	**Animal #**	**PDAPP Staining**	**Vaccine**	**Animal #**	**PDAPP Staining**
CRM/ Aβ 1-5	1	+(no diffuse)	CRM/ Aβ 1-5	1	-
	2	++/+++		2	-
	3	++/+++		3	±
	4	++		4	±
	5	++		5	±
CRM/ Aβ 1-7	1	++	CRM/ Aβ 1-7	1	+
	2	++		2	++
	3	++		3	++
	4	++		4	+
	5	++		5	++
CRM/ Aβ 1-9	1	+	CRM/ Aβ 1-9	1	++
	2	+/++		2	++
	3	±		3	+
	4	±		4	+
	5	±		5	+
CRM/ Aβ 1-12	1	-	CRM/ Aβ 1-12	1	+
	2	?		2	+
	3	±		3	++
	4	-		4	-
	5	±		5	±
CRM/ Aβ 12-1mer	1	-	Aβ42	1	-
	2	-		2	-
	3	±		3	-
	4	-		4	-
	5	±		5	-

All antiserum diluted 1:1000 for staining procedure.

Table 7B. PDAPP mouse brain tissue staining.

30 µg Dose					
Without Linker			With Linker		
Vaccine	**Animal #**	**PDAPP Staining**	**Vaccine**	**Animal #**	**PDAPP Staining**
CRM/ Aβ 1-5	1	-	CRM/ Aβ 1-5	1	+
	2	+/++		2	-
	3	-		3	-
	4	±		4	±
	5	++		5	-
CRM/ Aβ 1-7	1	+/++	CRM/ Aβ 1-7	1	+
	2	++		2	±/+
	3	++		3	+/++
	4	++		4	±/+
	5	++/+++		5	+/++
CRM/ Aβ 1-9	1	++/+++	CRM/ Aβ 1-9	1	+/++
	2	++		2	++
	3	++		3	++
	4	+		4	±
	5	+		5	+/++
CRM/ Aβ 1-12	1	-	CRM/ Aβ 1-12	1	+/++
	2	+/++		2	+
	3	+/++		3	-
	4	±		4	+/++
	5	±		5	+
CRM/ Aβ 12-1mer	1	-	Aβ 42	1	±
	2	-		2	-
	3	-		3	-
	4	-		4	-
	5	-		5	-

All antiserum diluted 1:1000 for staining procedure.

EXAMPLE 7

Immunogenicity Studies in Monkeys